



eBRAIN-Health

Public report

D9.2 Demonstrator Subclass Identification

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1. eBRAIN-Health

The Project eBRAIN-Health is dedicated to creating a comprehensive distributed research platform that models and simulates the intricate neurobiological processes underlying human brain function and dysfunction, all within a secure, data-protection-compliant environment. This groundbreaking initiative, which is a result of collaborative efforts, aims to provide access to thousands of multilevel virtual brains from patients and healthy controls, thus fostering significant advancements in research and innovation. By integrating and preprocessing brain data from various sources, eBRAIN-Health addresses the critical societal challenge of dementia through a collaborative and interdisciplinary approach. A central goal of this project is the development of a digital twin for dementia, which will simulate complex neurobiological processes and serve as a vital resource for research communities. The eBRAIN-Health-Cloud will offer comprehensive services for personalized brain modeling and simulations across distributed e-infrastructures, ensuring data protection by design and default. This includes providing simulation-ready, multiscale brain data encompassing molecular (genomics, proteomics, metabolomics) and cellular levels, electrophysiology, imaging, behavioral, clinical, lifestyle, environmental data, and data from wearables. All brain data will be preprocessed and annotated to relate to a standard reference 3D brain space, enhancing their utility and accessibility.

Alzheimer's disease (AD) presents a pressing and urgent need for such an advanced platform. As a leading cause of dementia, AD affects millions worldwide, with its incidence expected to rise significantly as populations age. Current diagnostic methods and treatments are limited, often failing to detect the disease in its early stages or halt its progression effectively. This underscores the necessity for innovative approaches in AD research. The eBRAIN-Health platform aims to address this gap by providing tools to predict disease onset and progression through advanced modeling and simulation techniques. By integrating diverse data types — from molecular signatures to clinical assessments and neuroimaging — researchers can better understand AD pathophysiology and identify potential biomarkers for early detection and targeted therapy.

2. eBRAIN-Health consortium

- CHARITE – Universitaetsmedizin Berlin, Germany
- EBRAINS, Belgium
- Forschungszentrum Juelich GmbH, Germany
- Stichting Radboud Universiteit, Netherlands
- Universidad Pompeu Fabra, Spain
- OSLO Universitetssykehus, Norway
- tp21 GMBH, Germany
- Fraunhofer Gesellschaft zur Foerderung der Angewandten Forschung eV, Germany
- INDOC RESEARCH EUROPE gGmbH, Germany
- Universitaet Wien, Austria
- Universidad Complutense de Madrid, Spain
- EODYNE Systems SL, Spain
- ATHENA – Research and Innovation Center, Greece
- University of Oslo, Norway
- Universita degli Studi di Roma la Sapienza, Italy
- Alzheimer Europe, Luxembourg
- Institute National de Recherche en Informatique et Automatique, France
- Centre Hospitalier Universitaire Vaudois, Switzerland

- The University of Edinburgh, United Kingdom

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3. Introduction

AD stands as a prime example of a multifactorial disorder within the broader field of neurodegeneration, characterized by its complex etiopathogenesis that has hindered the development of effective treatments. Dementia, in its various forms, stems from multiple causes, with Alzheimer's disease being the most prevalent yet enigmatic due to its myriad contributing factors. The pathology of AD involves a constellation of elements such as amyloid-beta accumulation (Hardy and Selkoe 2002), tau protein tangles (Goedert, Klug et al. 2006), vascular damage (Kalaria 2010), neuroinflammation (Heneka, Carson et al. 2015), network disruption (Stam 2014), excitotoxicity (Palop and Mucke 2010), impaired synaptic plasticity (Selkoe 2001), and disturbed growth factor signaling (DeKosky and Scheff 1990), among others.

Given this diversity in underlying mechanisms, the term "Alzheimer's Disease" is increasingly seen as an umbrella term that likely encompasses a variety of etiologically distinct subtypes. This heterogeneity is encapsulated in the ATN classification proposed by (Jack, Bennett et al. 2018), which categorizes AD biomarkers into three groups: amyloid plaques (A), tau pathology (T), and neurodegeneration (N). This framework underscores the importance of a multidimensional approach to understanding and classifying AD, highlighting the potential for distinct subtypes based on differing combinations of these pathological markers.

There is a pressing need for comprehensive models that integrate these diverse factors to address the complexity of AD. Recent advancements propose the development of computational whole-brain models, such as the one suggested by (Cabrera-Álvarez, Stefanovski et al. 2024). These models utilize a complex closed-loop design to simulate the dynamics of amyloid-beta and tau proteins, which, in turn, affect whole-brain activity by disrupting the excitation-inhibition balance, leading to excitotoxicity. This disruption contributes further to protein pathology, creating a vicious cycle of neurodegenerative processes.

This closed-loop modeling approach not only elucidates the interplay between amyloid-beta and tau but also facilitates the identification of distinct spatial subtypes of AD. By examining the cascading effects of initial protein distributions within a mechanistic framework, researchers can explore different AD subtypes' potential trajectories and outcomes. Such insights are invaluable for understanding how early-stage Braak pathology can predict subsequent proteinopathy (Braak and Braak 1991) and how atypical protein distribution patterns might manifest in the brain.

In summary, the multifactorial nature of Alzheimer's disease, encompassing a broad spectrum of pathological processes, necessitates advanced integrative models to unravel its complexity. However, by leveraging computational approaches to simulate the intricate dynamics of amyloid-beta and tau within the brain, researchers can gain a deeper understanding of the disease's subtypes and progression. This understanding holds promise for developing more targeted and effective therapeutic strategies to combat this devastating condition, instilling a sense of hope in the audience.

4. Partners involved

5. Description of work performed

This demonstrator is based on the work by Cabrera-Álvarez et al. (Cabrera-Álvarez, Stefanovski et al. 2024). The study is published under open access conditions according to a CC-BY 4.0 license, which allows the reproduction in this report. For details on the license, please refer to <https://creativecommons.org/licenses/by/4.0/>.

Herein, we focus on subclass identification in Alzheimer's disease, particularly exploring the spatial types of protein distribution and their effects on neural dynamics. The aforementioned study integrated multiple sophisticated neuroimaging and computational techniques to analyze and simulate the progression of AD at different scales, from molecular interactions to large-scale brain network dynamics.

Data acquisition involved magnetic resonance imaging (MRI) of 20 healthy participants to establish a baseline for comparison. Diffusion-weighted imaging (DWI) captured detailed structural connectivity (SC) metrics, such as tract lengths and connection weights between brain regions. These metrics were then used to construct brain network models (BNMs) that were the backbone for simulating neural activity and disease progression.

The study utilized a closed-loop neurotoxicity model that integrates the propagation of amyloid-beta ($A\beta$) and hyperphosphorylated tau (hp-tau) proteins within the brain (**Figure 1**). This model is based on the heterodimer hypothesis, where the interaction between healthy and toxic protein isoforms leads to the spread of neurotoxic effects. These proteins' production, clearance, and transformation rates were parameterized, and their spatial diffusion was modeled using the brain's structural connectivity matrix. Additionally, the model incorporated the effect of neural hyperactivity on producing and propagating toxic proteins.

The spatiotemporal profile of protein propagation was assessed by mapping the concentration of toxic proteins across different brain regions over time, using the Braak staging system as a reference. Various seeding strategies for $A\beta$ and hp-tau were simulated to explore their impact on disease progression, including fixed and randomized seeding patterns. The temporal differentiation between anterior and posterior regions in terms of neural firing rates and functional connectivity (FC) was also analyzed.

To capture the electrophysiological changes associated with AD, the study employed the Jansen-Rit neural mass model (JR-NMM) (Jansen and Rit 1995), simulating cortical column oscillatory activity. This model was adapted to include parameters reflecting the impact of $A\beta$ and hp-tau on synaptic transmission. The disruption of GABAergic synapses by $A\beta$ and the loss of dendritic spines due to hp-tau were specifically modeled to reflect their respective contributions to neural hyperactivity and silencing.

Functional measures, such as spectral frequency, power, and phase locking value (PLV), were derived from the simulated neural activity to validate the model against empirical observations. The parameter

spaces were explored iteratively to reproduce key pathological features of AD, such as the slowing of alpha frequency, the rise and fall of relative alpha power, and changes in FC.

Overall, this comprehensive methodological framework allows for the detailed analysis of protein distribution patterns and their effects on brain function in AD, providing insights into the mechanisms driving disease progression and potential targets for therapeutic intervention.

6. Results

The results presented in the study by Cabrera-Álvarez et al. highlight critical insights into the mechanisms of AD, particularly focusing on the impact of A β and hp-tau proteins on neural activity and the progression of the disease. The researchers employed a mechanistic multiscale model that integrates the JR-BN) to simulate the evolution of AD by linking protein propagation to changes in neural activity.

The findings indicate that the disruption of inhibitory synapses, primarily due to A β , plays a significant role in the electrophysiological changes observed in AD. This disruption leads to a reduction in GABAergic synapses, which in turn causes neural hyperactivity near amyloid plaques. This conclusion is supported by previous studies showing that reduced GABAergic synaptic activity is directly associated with hyperactivity near amyloid plaques. The model favors the hypothesis that the lowering of inhibition (related to GABAergic synapses' disruption) over the rising of excitation (related to impaired glutamate reuptake) better explains the characteristic hyperactivity produced by toxic A β on neural tissue.

To differentiate the contributions of A β and hp-tau independently, we isolated the effects of each protein on the model's inhibitory parameters (**Figure 2**). The results showed that A β had a more pronounced and earlier impact on inhibition compared to hp-tau, which had a delayed and shorter duration effect. This differential timing suggests a complex interplay between A β and hp-tau in driving the neural dynamics of AD.

The study also explored the spatiotemporal profiles of AD progression based on different initial locations of A β and hp-tau depositions (**Figure 3**). Four seeding strategies were tested: fixed seeding, A β -random seeding, hp-tau-random seeding, and random seeding for both proteins. Fixed and A β -random seeding strategies effectively reproduced the Braak stages, which describe the progression of tau pathology in AD. In contrast, randomizing both A β and hp-tau seeding locations resulted in more diverse Braak sequences, highlighting the importance of initial seeding locations in disease progression.

Additionally, the researchers investigated the antero-posterior differentiation in neurophysiological changes along the AD continuum by randomizing the seeding of A β and hp-tau. The findings revealed a stable precession of posterior regions regarding firing rate, regardless of the seeding location, indicating that hyperactivity tends to emerge earlier in these regions. However, functional connectivity (FC) differentiation was more influenced by A β seeding. Anterior seeding led to earlier peaks in anterior regions. In comparison, posterior seeding caused earlier peaks in posterior regions, suggesting that the spatial origin of A β seeding significantly affects the temporal progression of neural activity changes.

In summary, the study demonstrates the intricate relationship between protein distribution and neural activity in AD, emphasizing the critical role of inhibitory disruption and the spatiotemporal dynamics of protein seeding in shaping the disease's progression. These insights provide a valuable framework for understanding the molecular and electrophysiological mechanisms underlying AD and may guide future therapeutic strategies to target these critical pathological processes.

7. Conclusion, next steps

In conclusion, this study presents a comprehensive mechanistic model for subclass identification in AD, focusing on the spatial distribution of A β and hp-tau proteins. Our model allows for a detailed analysis of these proteins' spatial distribution, offering insights into their roles at various levels including excitation and inhibition balance, excitotoxicity, and pathological conformation building.

Our findings demonstrate that early Braak stages result in typical protein distribution, primarily influenced by impaired inhibition. Specifically, we observed that Abeta seems to modulate inhibitory impairment, and early Braak stages can predict subsequent proteinopathy. These results align with established neuropathology models, which estimate Abeta and Tau distribution based on observed proteinopathies. Moreover, our model enables the exploration of atypical protein distribution subtypes, enhancing our understanding of cognitive disease subtypes based on spatial profiles obtained from MRI, PET, EEG, and other imaging modalities.

The model's ability to distinguish between different cognitive disease subtypes and understand atypical AD variants, such as posterior cortical atrophy (PCA), primary progressive aphasia (PPA), and behavioral AD, is particularly noteworthy. This capability is crucial for developing personalized treatment strategies and improving diagnostic accuracy.

Our future steps involve validating the model with atypical AD variants and individual patient data, including cases with varying progression rates, conversion to later stages, and treatment responses. We will leverage multimodal data available in the eBrain-Health consortium for these purposes. This validation will help refine our model and reveal new insights into AD progression and treatment efficacy.

The insights gained from our model underscore the importance of neural inhibition in AD progression. Our results suggest that the disruption of inhibition, primarily driven by Abeta effects, plays a critical role in the electrophysiological alterations observed in AD. Additionally, we identified a temporal dissociation between hyperactivity and interregional hypersynchrony, challenging previous assumptions about their direct linkage.

Our multiscale closed-loop neurotoxicity model provides a robust framework for understanding AD progression. It integrates molecular, cellular, and network-level changes, offering a holistic view of AD mechanisms. This model holds promise for advancing our knowledge of AD pathophysiology, guiding the development of novel therapeutic interventions, and enhancing early detection and personalized care in Alzheimer's disease. As highlighted by our research, continued efforts in computational modeling and data integration are essential for unraveling the complexities of AD and improving patient outcomes.

8. Figures and Tables

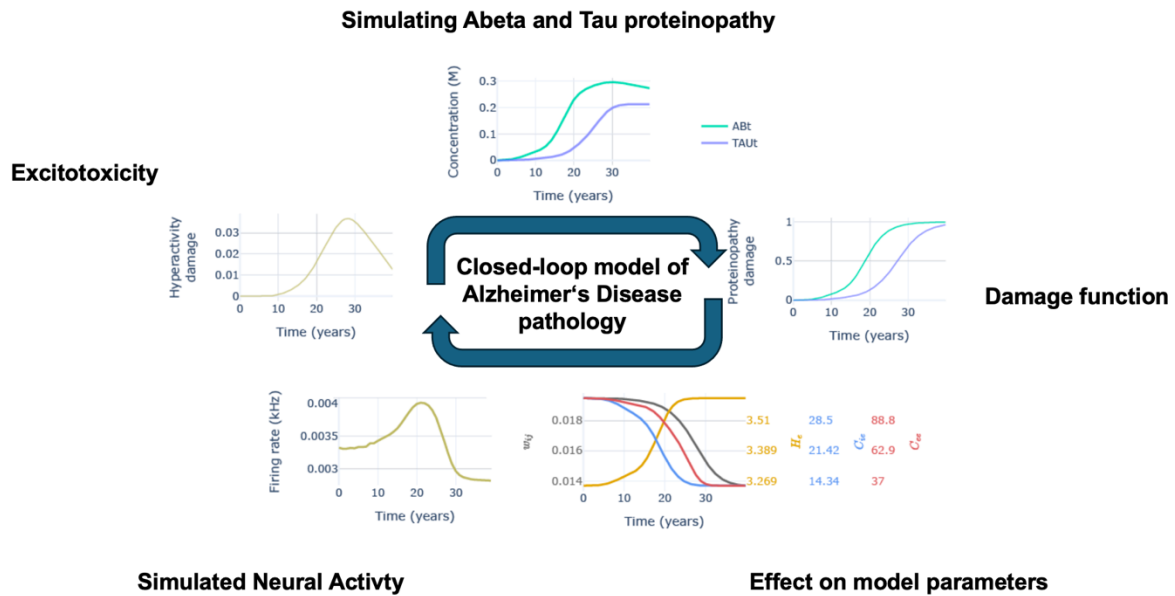


Figure 1. Schematic representation of the closed-loop model of Alzheimer's Disease pathology, highlighting the simulation of A β and Tau proteinopathy over time. Starting from simulating A β and Tau concentration and distribution based on molecular assumptions, it uses these to integrate their effects on dynamic model parameters through a damage function. The resulting neural activity is further used to assess exceeding excitation, which is re-affecting the protein pathology via the mechanism of excitotoxicity. The whole model can simulate the dynamics of Alzheimer's Disease on multiple levels over a large timeframe of more than 30 years. This figure contains modified elements from (Cabrera-Álvarez, Stefanovski et al. 2024), which is published under open access conditions according to a CC-BY 4.0 license: <https://creativecommons.org/licenses/by/4.0/>.

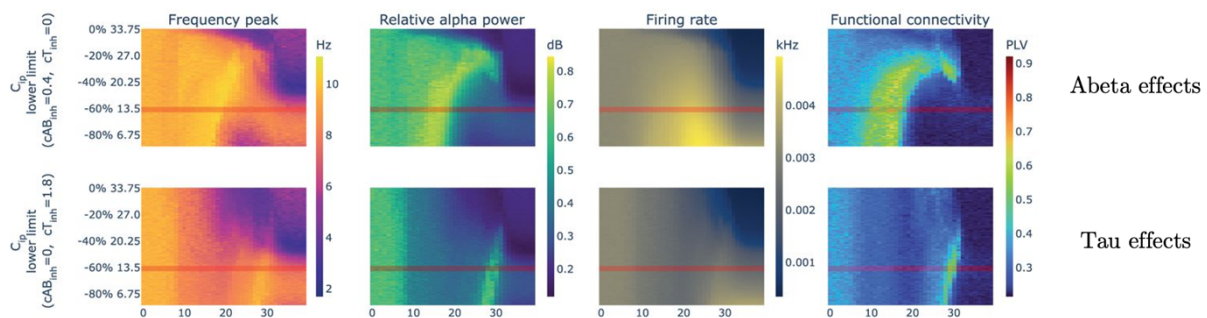


Figure 2. Heatmaps showing the differential influence of A β and Tau parameters on various functional metrics over time. The metrics include frequency peak, relative alpha power, firing rate, and functional connectivity. The top row represents the effects of A β , while the bottom row represents the effects of Tau. The color scale indicates the intensity of each metric, with specific parameter settings noted on the left. As it can be seen, the A β bias parameter controls the effect of inhibition on the system over time, while the Tau parameter does not express a major effect in this analysis. This figure contains modified elements from (Cabrera-Álvarez, Stefanovski et al. 2024), which is published under open access conditions according to a CC-BY 4.0 license: <https://creativecommons.org/licenses/by/4.0/>.

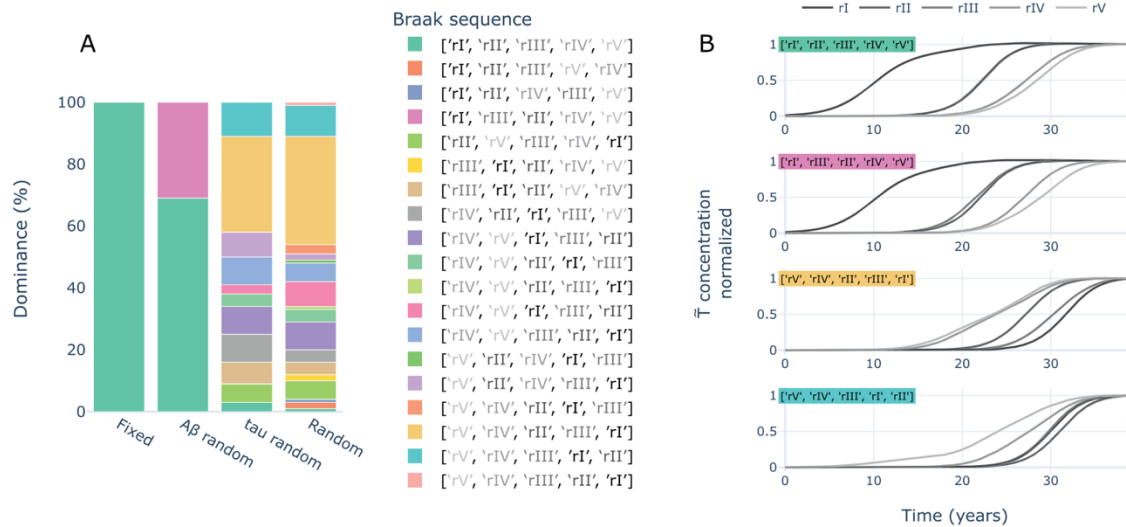


Figure 3. Detailed analysis of spatiotemporal profiles in Alzheimer's Disease (AD). Panel A shows the dominance of Braak sequences under different conditions: fixed, A β random, Tau random, and completely random. Each color represents a distinct Braak sequence, with sequences detailed on the right. While the fixed (i.e., typical) seeding leads stably to the traditional Braak sequence (I-V) and the same holds true for randomized A β seeding, any randomization of Tau seeds leads to completely different spatiotemporal profiles. In panel B, the most common (typical and atypical) profiles are depicted by their normalized Tau concentration over time for selected Braak sequences. Each subplot corresponds to a different Braak sequence from panel A, showing the progression of Tau accumulation across different brain regions (rI to rV) over 30 years. This allows the identification and further investigation of spatiotemporal subgroups of AD, which are mechanistically deduced from the dynamics inside the closed-loop model. This figure contains modified elements from (Cabrera-Álvarez, Stefanovski et al. 2024), which is published under open access conditions according to a CC-BY 4.0 license: <https://creativecommons.org/licenses/by/4.0/>.

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